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1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,897	VADAS ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-17,23-31,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8-17,23-30,36 and 37* is/are rejected.

7)☒ Claim(s) *31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 8-17, 23-31 and 36-37 are presented for examination.

Applicant's Amendment filed July 31, 2007 has been received and entered into the present application.

Claims 1-2, 8-17, 23-31 and 36-37 are pending and under examination. Claims 3-7, 18-22 and 32-35 are cancelled and claims 1-2, 8, 14-17, 23 and 29-31 are amended.

Applicant's arguments, filed July 31, 2007, have been fully considered. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and objections are either reiterated or newly applied. They constitute the complete set of rejections and objections presently being applied to the instant application.

Withdrawal of Claim 31 for Improper Multiple Dependency (New Ground of Objection)

Claim 31 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Please see MPEP §608.01(n). **Accordingly, claim 31 has not been further treated on the merits.**

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 8-13, 16-17 and 23-28 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record set forth at pages 3-8 of the previous Office Action dated January 31, 2007, of which said reasons are herein incorporated by reference.

Applicant traverses the present rejection, stating that sphingosine kinase is a molecule that has been extensively characterized structurally and functionally and, accordingly, agents that downregulate sphingosine kinase activity, and classes of agents in this regard (e.g., those listed at page 6 of Applicant's remarks), are well known and have been extensively described in the art. Applicant further states that those agents that are not yet known could be identified without undue experimentation. Applicant further relies upon the fact that the specification identifies specific agents exhibiting the desired sphingosine kinase modulating property and exemplary classes of agents that one might utilize in the present invention.

Applicant's remarks have been fully and carefully considered in their entirety, but fail to be persuasive.

First, Applicant is reminded that rejections under the written description requirement of 35 U.S.C. 112, first paragraph, are set forth when the claim scope is not commensurate with what is disclosed, and, therefore, what was in possession of the Applicant at the time of the invention, in the accompanying specification. In the instant case, while generic techniques such as Western blotting or electrophoretic mobility shift assays were techniques that could have been employed during screening for agents capable of downregulating sphingosine kinase to detect their modulating ability, it is the very fact that both Applicant's remarks and the instant specification are clearly indicative of the fact that the skilled artisan would have been required to execute extensive testing in a variety of different compounds (in fact, conceivably all compounds, in the absence of any guidance or direction as to a subset of compounds that would, at the very least, have been reasonably expected to have such a downregulating or antagonizing effect on the activity of sphingosine kinase based on, e.g., structural characteristics, etc.), to determine if such compounds actually modulated, i.e., downregulated, the activity of sphingosine kinase.

It is this very need for testing amongst widely varying species of compounds to determine the full scope of the genus of agents capable of downregulating the activity of sphingosine kinase that is clearly

demonstrative of the fact that Applicant was not in possession of the full scope of this genus of agents presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please reference MPEP §2163.

Applicant discloses two actual compounds that are capable of acting as sphingosine kinase antagonists, i.e., N,N-dimethylsphingosine or DL-threo-dihydrosphingosine (page 15, lines 15-16). However, aside from this disclosure, Applicant provides only teachings of multiple generic functional classes of agents capable of downregulating the activity of sphingosine kinase, including (1) agents that modulate the expression of sphingosine kinase DNA or RNA, e.g., antisense RNA, ribosomes, DNA enzymes, microRNAs, molecules suitable for use in cosuppression, (2) antagonists of the sphingosine kinase expression product, e.g., antibodies, nucleic acid aptamers, dominant negative sphingosine kinase variants, (3) agents that modulate the catalytic activity of sphingosine kinase by competing with its substrate, wherein the substrate is, e.g., sphingosine kinase or ATP, (4) agents that interfere with the catalytic activity of sphingosine via an allosteric mechanism, or (5) agents that interfere with sphingosine kinase enzyme activation, such as those which modify phosphorylation or lipid composition, those which are coupled in a non-covalent manner to a required co-activator of the enzyme or those which modulate the subcellular localization of the enzyme.

Despite the disclosure of various functional classes of agents, it remains that the specification provides non-limiting exemplification of solely functional genera of agents that may be used within the context of the present invention. Applicant, in fact, admits on the record that this is "non-limiting exemplification" at page 6 of the remarks. With the exception of the two disclosed agents N,N-dimethylsphingosine or DL-threo-dihydrosphingosine, Applicant is imposing the burden of extensive

testing upon the skilled artisan to identify those other agents that may have any of the disclosed functions, but which Applicant has not identified and, thus, was not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicant may have a *plan* for how to identify other agents that may be amenable for use in the present invention, it remains that *at the time of the invention*, Applicant had not identified such compounds, and, therefore, did not have written description of the full scope of the genus claimed.

Further, though Applicant has limited the claimed agents to those that perform a particular function, e.g., those that antagonize sphingosine kinase expression, etc., it remains that Applicant has not appropriately defined the metes and bounds of the genus, even when limited by function. Adequate description of a functional step may be provided if the written description adequately links or associates an adequately described particular structure, material, or act to the function or if it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts would perform the function. The instant application does not meet either of these criteria. The present specification provides no disclosure beyond the generic disclosure of the required function that would correlate a common structural element or material to performance of the claimed function and that would be readily identifiable to one of skill in the art.

Additionally, it is noted that Applicant's exemplary classes of agents comprise agents with such substantial variation that the actual exemplification of two specific, tangible agents (i.e., N,N-dimethylsphingosine or DL-threo-dihydrosphingosine) is clearly not a number or selection of species that

is representative of the entire breadth of agents encompassed by the genera of agents presently claimed. For example, Applicant's specification clearly states that the claimed agents encompass organic compounds, antigens, RNA, ribosomes, DNA enzymes, microRNAs, RNA aptamers, antibodies, and dominant negative sphingosine kinase variants, among others, which is clearly indicative of substantial variation within the claimed genus. In accordance with the written description requirement of 35 U.S.C. 112, first paragraph, substantial variation that exists within a large and highly varied genus of compounds requires at least a description of a representative number of species of the genus in order to satisfy the requirement, of which Applicant has only provided two such species. It has been held that when there is substantial variation within a genus that one must describe a sufficient variety of species *to reflect the variation within the genus*. Given that Applicant has placed essentially no limitation on the identity of the compounds within the genus of those that are capable of downregulating sphingosine kinase activity, the disclosure of two species fails to represent a variety of species that would reflect the substantial variation clearly present within the claimed genus. Accordingly, the disclosure fails to demonstrate that Applicant was actually in possession of the entire genus of agents capable of the claimed function.

Further, it is noted that Applicant alleges throughout the remarks that the claimed class(es) of agents capable of downregulating sphingosine kinase activity are well known and have been extensively described in the art (see, e.g., page 5 of the remarks), but provides no evidence in support of such an allegation. Accordingly, such remarks are no more than allegations without factual support. As set forth in MPEP §2145, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

For the reasons provided *supra*, the claims continue to fail to meet the written description requirement set forth under 35 U.S.C. 112, first paragraph, and the present rejection of claims 1-2, 8-13, 16-17 and 23-28 is properly **maintained**.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 8-17, 23-30 and 36-37 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing the concentration of Ras-transformed fibroblasts (in which Ras expression is upregulated) by down-regulating the activity of sphingosine kinase (SphK) using dimethylsphingosine or reducing the proliferation of human breast adenocarcinoma cells by down-regulating the expression of SphK using dimethylsphingosine, does not reasonably provide enablement for the modulation of the growth of any neoplastic call, particularly any malignant neoplastic cell, using any agent that modulates the functional activity of SphK, nor does the specification reasonably provide enablement for the treatment or prophylaxis of any condition characterized by neoplastic cell proliferation, particularly malignant neoplasm, for the reasons of record set forth at pages 10-18 of the previous Office Action dated January 31, 2007, of which said reasons are herein incorporated by reference.

Instant claim 31 has been removed from the present rejection since the claim is now improperly multiply dependent and has been withdrawn from consideration.

Applicant traverses the present rejection, stating that Applicant questions the relevance of the six-year-old textbook (i.e., Cecil's Textbook of Medicine), since "textbooks are themselves known to often be significantly out of date" and that Applicant questions "how an out of date text could be used to suggest that the present invention cannot support an important finding in relation to neoplastic cells, being that in the context of oncogene induced neoplasms, the downregulation of sphingosine kinase is effectively reducing proliferation." Applicant further submits that the argument(s) presented by the Examiner are in direct contrast to the arguments raised by the Examiner in the context of anticipation and obviousness,

where the Examiner has argued that "RAS oncogenic activity was so well known as a robust and most frequently activated oncogene in all forms of cancers." Applicant states, "In light of the teachings in the specification there is no reason why the skilled person would not accept that the finding of the oncogenic activity of sphingosine kinase does not represent a significant step forward in terms of the treatment of neoplasms", and further relies upon the fact that (1) the cell model used in the present application is "a well recognized and accepted *in vitro* model of neoplasia" and (2) according to the MPEP, an *in vitro* model example can constitute a working example if that example correlates with a disclosed or claimed method invention.

Applicant's remarks have been fully and carefully considered in their entirety, but fail to be persuasive.

First, Applicant's remarks regarding the "relevance" of the "out-of-date" texts cited by the Examiner are clearly not persuasive. It is noted that a conclusion of a lack of enablement must take into consideration *the unpredictability in the art at the time of the invention and the direction or guidance provided by Applicant.* Accordingly, the citation of Cecil's Textbook of Medicine is clearly relevant because Cecil's shows that, even in 2000, which, it is noted, is *at or around Applicant's effective filing date and, thus, the "time of the present invention"*, not only had prevention of cancerous or neoplastic conditions still not been achieved, but that the use of a single agent for the generic treatment of any cancer or neoplastic condition also still had not been achieved at that time. In other words, the state of the art was sufficiently unpredictable in terms of cancer therapeutics *at the time of the invention* that Applicant's claim to treating any cancer or malignant neoplastic condition using any agent capable of downregulating sphingosine kinase activity would have been meet with great skepticism by one of ordinary skill in the art.

Second, regarding Applicant's assertion that "textbooks are themselves known to often be significantly out of date", Applicant provides absolutely no evidentiary basis to support his allegation

and, thus, such a statement is clearly an opinion and amounts to no more than an allegation without factual support.

Further, Applicant's allegation that the Examiner has contradicted her opinion on the state of the art between the enablement rejection and the prior art rejections under anticipation and obviousness is not persuasive because Applicant has taken the Examiner's remarks out of context. Applicant states that, "the Examiner argues that the present invention is not patentable in relation to any neoplastic cell on the basis that RAS oncogenic activity was so well known as a robust and most frequently activated oncogene in all forms of cancers." The Examiner has not asserted such facts on the record, but rather has stated that, in view of the teachings of Prashad, who expressly teaches the increased expression of Ras in, e.g., stomach, brain, bone, esophageal, pancreatic or ovarian carcinomas, one of ordinary skill in the art would have had the *reasonable expectation* that the same neoplastic conditions taught in Spiegel would also have demonstrated this same upregulated Ras expression. The prior art rejections did not assert, unsupported by evidence, that Ras oncogenic activity was known and, thus, would have been expected to be present in any cancer. Prashad expressly teaches Ras activity in those specific cancers that expressly overlap with those particularly set forth and presently claimed.

Additionally, the Examiner has not taken an inconsistent position on the state of the art. The art as taught by Spiegel further corroborates the Examiner's conclusion that the instant specification is enabled for reducing the proliferation of Ras-transformed fibroblasts by administering the compound dimethylsphingosine. Please see the Examples of Spiegel, who provides testing of sphingosine kinase activity in NIH 3T3 fibroblast cell lines (which are, in fact, identical to the fibroblast cell lines used in a number of Applicant's Examples), and also page 35, lines 7-32, which teaches the treatment of cancers of cartilage.

Regarding Applicant's statement that, "In light of the teachings in the specification there is no reason why the skilled person would not accept that the finding of the oncogenic activity of sphingosine

kinase does not represent a significant step forward in terms of the treatment of neoplasms", such a statement is immaterial to whether Applicant has provided adequate enabling direction for the *full scope of the claimed subject matter.* It is not disputed that the skilled artisan would have accepted the disclosed subject matter as relevant to the treatment of neoplasms, but the fact that Applicant has failed to provide sufficient enabling guidance or direction commensurate in scope with what is presently claimed is clearly indicative of a failure to meet the burden of describing how to make, use and/or practice the invention in its entirety as claimed.

Additionally, Applicant relies upon the cell model used in the present application as "a well recognized and accepted *in vitro* model of neoplasia", but provides no evidence or documentation, either in the remarks or in the specification, that teaches the claimed *in vitro* fibroblast cell model as a "well-recognized and accepted" model of any neoplasia. Accordingly, such a remark is no more than an allegation without factual support. As set forth in MPEP §2145, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

Lastly, though the Examiner does not disagree with the statement that an *in vitro* model example can constitute a working example if that example correlates with a disclosed or claimed method invention, it remains that the disclosed *in vitro* working example does *not* correlate to the scope of the claims for the reasons previously set forth in the Office Action of January 31, 2007 at pages 10-18, which will not be repeated herein so as not to burden the record. Applicant further provides no evidence in support of the allegation that the *in vitro* model used is, in fact, representative of *all neoplasias*, and, accordingly, such an argument is clearly not persuasive.

For the reasons provided *supra*, and those previously made of record at pages 10-18 of the Office Action dated January 31, 2007, the rejection remains proper and is hereby **maintained**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 8-17, 23-30 and 36-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Spiegel (WO 99/61581; 1999) in view of Prashad (U.S. Patent No. 5,068,175; 1991), each already of record, for the reasons of record set forth at pages 21-23 of the previous Office Action dated January 31, 2007, of which said reasons are herein incorporated by reference.

Instant claim 31 has been removed from the present rejection since the claim is now improperly multiply dependent and has been withdrawn from consideration.

Applicant traverses the present rejection, stating that Spiegel teaches the modulation of largely normal cellular functioning and asserts that Spiegel is not enabling on the grounds that the specification provides "no teaching or support in relation to the notion of sphingosine kinase functionality in the context of oncogenic neoplastic cells" and relies upon the fact that the only example provided in Spiegel relates to hyperproliferative conditions, which is a distinct cellular proliferation mechanism than neoplastic proliferation. Applicant asserts that Spiegel fails to teach neoplastic cells, but rather teaches

hyperproliferative cells, which are separate and distinct cell types (see, e.g., page 11 of Applicant's remarks). Applicant alleges that the present invention is not limited to the downregulation of cell proliferation in which RAS is functioning as an oncogene, but rather that, even in the presence of other oncogenes, sphingosine kinase nevertheless exhibits increased activity and that its oncogenic activity, either together with another oncogene or in isolation, provides an appropriate target for treatment. Applicant further states that the Examiner has impermissibly used hindsight in making the present rejection and asserts that Prashad fails to disclose or suggest that sphingosine kinase play a role in oncogenic transformation or that it can function as an oncogene.

Applicant's remarks have been fully and carefully considered in their entirety, but fail to be persuasive.

First, it is noted that Applicant's subjective characterization of the reference as teaching "largely normal cellular functioning" is, in fact, factually incorrect. Spiegel still clearly, expressly and deliberately teaches a method for treating or ameliorating a disease resulting from an increase in cellular proliferation, such as cancer, by providing to an individual in need of such treatment an effective amount of an agent that inhibits SPHK expression or function in a pharmaceutically acceptable excipient, wherein the compound is implanted for release at the site of the tumor, and further wherein the specific cancers of lung, stomach, ovarian, pancreatic, esophageal, brain or bone sarcoma may be treated. This is clearly contradictory to Applicant's allegation that the reference teaches the modulation of "largely normal cellular functioning", because it is evident that a cancerous or neoplastic cell is obviously not functioning "normally". Please see Spiegel at p.8, l.27-34, p.36, l.22-27, p.35, l.7-32 and p.38, l.2-7.

Second, with regard to Applicant's assertion that the reference to Spiegel is not enabling because it fails to relate the functionality to sphingosine kinase in oncogenic neoplastic cells, this is also a factually incorrect statement. Spiegel's express teaching that the treatment of cancer can be effected via the administration of an agent that inhibits the function or expression of SPHK is clearly a correlation

between the function of sphingosine kinase and oncogenic neoplastic cells. Nevertheless, even if Spiegel did not provide such a correlation, it is noted that the validity of a disclosure does not rest on a requirement to explain a mechanism of action; a disclosure is valid for all that it would have suggested to one skilled in the art, whether such a mechanism was known or not at the time of the conception of the idea for using a pharmaceutical agent for the treatment of a particular disease state or condition.

Further, the fact that Spiegel provides an example in hyperproliferative cells and not neoplastic cells does not render the reference non-enabled because it fails to present a working or prophetic example of the administration of an SPHK inhibitor to a neoplastic cell. The enablement of a disclosure does not hinge on the presence of working or prophetic examples of an embodiment that is very clearly taught and, thus, contemplated by the reference. Please reference MPEP §2164.02, which states, "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed...The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)."

It is, therefore, erroneous and contradictory to the teachings of the MPEP for Applicant to completely discount the disclosure of Spiegel solely on the grounds that Spiegel has not provided a working example of the disclosed method(s). Furthermore, Applicant provides no evidence in support of the conclusion that the reference is not enabled, and, therefore, is alleging non-enablement in the absence of factual support. Please reference MPEP §716.01(c)[R-2](II), which states, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, *inoperability of the prior art*, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the

applicant." (emphasis added) In other words, it is insufficient to rely solely on Applicant's opinion of the reference without addressing the totality of evidence in the reference or in the record as a whole.

Applicant is further attempting to demonstrate a patentable distinction of the presently claimed invention over Spiegel by asserting that the disclosure teaches hyperproliferative cells, which proliferate via a different mechanism than neoplastic cells. While it may be true that hyperproliferative cells proliferate due to a stimulus, where neoplastic cells proliferate abnormally in the absence of a stimulus, this is immaterial to the fact that Spiegel still teaches the treatment of oncogenic neoplastic cancer cells, such as, e.g., lung, stomach, ovarian, pancreatic, esophageal, brain or bone sarcoma. Therefore, whatever "mechanism" by which they proliferate is irrelevant to the fact that Spiegel expressly teaches the treatment of neoplastic cells with an SPHK inhibitor. The Examiner appreciates the difference between the proliferative mechanisms, but again relies upon the clear and unequivocal teachings of Spiegel in support of the rejection, which clearly teaches the treatment of neoplastic cells via SPHK inhibition.

With regard to Applicant's allegation that the present invention is not limited to the downregulation of cell proliferation in which RAS is functioning as an oncogene, Applicant is reminded that the instant specification and examples disclose no other oncogenes aside from RAS and, therefore, the assertion that the downregulation of cell proliferation in which RAS is functioning as an oncogene is merely exemplary of the downregulating cell proliferation in neoplastic cells transformed by the activity of any other oncogene is unsubstantiated by any evidence and, accordingly, is unpersuasive. Applicant's further assertion that, even in the presence of other oncogenes, sphingosine kinase nevertheless exhibits increased activity and that its oncogenic activity, either together with another oncogene or in isolation, provides an appropriate target for treatment is also not found persuasive because Spiegel clearly acknowledges the increased activity of SPHK in cancerous or neoplastic cells and proposes the treatment of such cells with an inhibitor of SPHK. In other words, the prior art already appreciates the fact that sphingosine kinase activity is an appropriate target for treating cellular proliferation of neoplastic cells.

Regarding Applicant's assertion that the Examiner has used improper hindsight to arrive at the presently claimed invention, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Considering the fact that the present rejection under 35 U.S.C. 103(a) relies solely on the knowledge that was generally available to one of ordinary skill in the art at the time of the invention and does not improperly rely upon Applicant's disclosure, the assertion that the present rejection is made with impermissible hindsight reconstruction is not found persuasive.

Lastly, in response to Applicant's argument that Prashad fails to disclose or suggest that sphingosine kinase play a role in oncogenic transformation or that it can function as an oncogene, Applicant is clearly not addressing the combined teachings of the cited references as a whole, but rather is focusing solely on the discrete teachings of each of the cited references and asserts that, since Prashad does not teach the oncogenic activity or function of sphingosine kinase, that the rejection is improper. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references that make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the combination of the cited references. Please reference *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968) and *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For these reasons, and those previously set forth at pages 21-23 of the previous Office Action dated January 31, 2007, the instant rejection of claims 1-2, 8-17, 23-30 and 36-37 remains proper and is **maintained**.

Double Patenting

Applicant is advised that the provisional rejection of the instant claims over claims 1-5, 7 and 18-26 of copending U.S. Patent Application No. 10/531,626 has been hereby **withdrawn** in view of Applicant's amendments to the instant claims.

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2 and 8-17 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8-9, 11-15, 29 and 50-55 of copending U.S. Patent Application No. 10/275,686, for the reasons of record set forth at pages 23-25 of the previous Office Action dated January 31, 2007, of which said reasons are herein incorporated by reference.

Copending claim 49 has been cancelled and, thus, the instant rejection over such a claim is now rendered **moot**.

Applicant acknowledges the rejection and states that since copending U.S. Patent Application No. 10/275,686 has not been allowed, no further action is required at this time.

Applicant's remarks have been fully and carefully considered in their entirety. In the absence of a Terminal Disclaimer, or any arguments or evidence to the contrary, the rejection remains proper and is **maintained**.

Double Patenting (New Grounds of Rejection)

Applicant's Duty to Disclose Copending Applications

Applicant's attention is further directed to the MPEP at §2001.06(b)[R-2]:

"The individuals covered by 37 C.F.R. 1.56 have a duty to bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications which are "material to patentability" of the application in question." See *Armour & Co. v. Swift & Co.*, 466 F.2d 767, 779, 175 USPQ 70, 79 (7th Cir. 1972).

Insofar as Applicant's has failed to bring copending U.S. Patent Application No. 11/629,850 to the Examiner's attention as being relevant to the presently claimed subject matter, and further in view of the fact that the copending '850 application was not available for the Examiner to view at the time of the previous Office Action dated January 31, 2007, the following new double patenting rejection is set forth:

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 8-13, 16-17 and 23-28 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-4, 10-12, 15-20 and 31-41 of copending U.S. Patent Application No. 11/629,850 in view of Prashad (U.S. Patent No. 5,068,175; 1991).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims

because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the cited copending application are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims clearly provide for methods of downregulating sphingosine kinase activity via contacting a cell with an effective amount of an agent effective to downregulate the intracellular localization of sphingosine kinase, as well as methods for the treatment and/or prophylaxis of a condition characterized by aberrant, unwanted or otherwise inappropriate sphingosine kinase functional activity via administering to a mammal in need thereof an effective amount of an agent effective to downregulate the intracellular localization of sphingosine kinase, using an agent such as, e.g., those described in copending claims 31-41. The copending claims also clearly provide for the treatment and/or prophylaxis of uncontrolled cellular proliferation, such as neoplastic cell proliferation of a malignant neoplasm, such as, e.g., solid tumors of the colon, stomach, lung, brain, bone, esophagus, pancreas, breast, ovary or uterus.

Though the copending claims fail to explicitly state that the malignant neoplastic cell(s) have been transformed due to the up-regulation of the oncogene Ras, Prashad is cited for its teachings that the cellular oncogene, Ras, is one of the most frequently identified activated oncogenes that results in neoplastic cell growth following transformation from a proto-oncogene to an oncogene via one of the following mechanisms: (1) point mutations in the coding region, (2) amplification of genes or (3) chromosomal translocation. Prashad states, "Activation of ras oncogene causes an increase of ras specific protein (p21) in colon, colorectal, lung, mammary, neuroblastoma, prostate, ovarian, melanoma and bladder carcinomas (references omitted). Thus, one can readily deduce that the p21 ras oncogene protein is a powerful tumor marker." Please see Prashad at col.1, l.37-58. It is clear from this teaching that it would have been *prima facie* obvious to one of ordinary skill in the art that the colon, lung, brain, breast

or ovarian carcinomas of the copending claims would have been reasonably expected to have resulted from the transformation from a physiologically normal cell to a neoplasm due to the up-regulation of Ras, which was well known in the art at the time of the invention to be a tumor marker expressly associated with these specific cancer types.

Accordingly, rejection of claims 1-2, 8-13, 16-17 and 23-28 is proper over claims 2-4, 10-12, 15-20 and 31-41 of copending U.S. Patent Application No. 11/629,850 as claiming obvious and unpatentable variants thereof. This is a provisional rejection because the claims have not yet, in fact, been patented.

Conclusion

Rejection of claims 1-2, 8-17, 23-30 and 36-37 remains proper and is **maintained**.

Claim 31 is **withdrawn** from consideration due to its improper multiple dependency.

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

October 8, 2007

Ardin H. Marschel 10/9/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER